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FULL PAPER

β-Selective glycosylation using *O*-aryl protected glycosyl donors

Yuji Otsuka, [a, b] Toshihiro Yamamoto, [a, b] and Koichi Fukase*[a]

Abstract: Novel glycosyl donors possessing several para-substituted *O*-aryl protecting groups that are introduced using diaryliodonium triflate have been developed, and their glycosylation stereoselectivity was evaluated. β-Selective glycosylation was achieved using thioglycosides protected by 4-nitrophenyl (NP) groups. Analysis of the stereoselectivity of several glycosyl donors indicated that β-glycosides are obtained through an S_N2-like displacement from the corresponding α-glycosyl triflate. The NP group can be removed by reduction of the nitro group and acylation, followed by ammonium hexanitratocerate (IV) (CAN) oxidation.

Introduction

Stereoselective *O*-glycosylation has attracted great attention for the efficient synthesis of oligosaccharides.[1] The most widely used method for stereoselective glycosylation is based on the neighboring group participation of the 2-*O*-acyl functionality. However, this protection is unpredictably accompanied by various side reactions, such as the formation of glycosyl orthoesters and migration of the acyl group to both the anomeric center and the glycosyl acceptor. To overcome this issue, various methodologies have been developed for the efficient and stereocontrolled synthesis of oligosaccharides using different 2-*O*-protecting groups. 2-*O*-ortho-cyanobenzyl,[2] 2-*O*-ortho-nitrobenzyl,[3] and 2-*O*-picolyl groups[4] have been used for 1,2-*trans* glycosylation, and several sulfide auxiliaries[5] as well as intramolecular aglycon delivery (IAD)[6] are applicable to 1,2-*cis* glycosylation reactions. The use of *O*-aryl groups for hydroxy protection has rarely been explored because of the lack of suitable protection methods (Figure 1). Recently, several synthetic methods for the *O*-arylation of carbohydrates have been reported, which provides access to the obtained arylated carbohydrates as unprecedented derivatives of biomolecules and glycosyl donors.[7-10] Herein, we describe the first use of *O*-aryl groups as stereodirecting substituents for the formation of the 1,2-transglycosidic linkage.

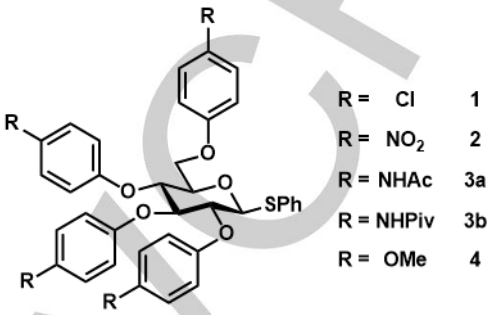

Figure 1. Structure of *O*-arylated glycosyl donors.

Results and Discussion

To investigate the effect of the presence of para-substituents in the aryl groups on the stereoselectivity of glycosylation, we synthesized four different glycosyl donors (Scheme 1). Tetra-*O*-4-chlorophenylated thioglycoside **1** was synthesized from compound **5** by using bis(4-chlorophenyl)iodonium triflate and Cs_2CO_3.[7] Tetra-*O*-4-nitrophenylated thioglycoside **2** was prepared using 4-nitrophenylphenyliodonium triflate and *t*BuOK, and tetra-*O*-4-acetamidophenylated thioglycoside **3a** and tetra-*O*-4-pivaloylaminophenylated thioglycoside **3b** were obtained from **2** by reduction of the nitro group and subsequent acylation. Pivaloylaminophenylated derivative **3b** was soluble in dichloromethane, whereas acetamidophenylated donor **3a** was not soluble in dichloromethane and, therefore, could not be used for the glycosylation reaction. Finally, tetra-*O*-4-methoxyphenylated thioglycoside **4** was synthesized from thioglycoside **1** by Pd catalyzed Buchwald methoxylation method.[11]

The stereoselectivity of the glycosylation was then investigated using benzyl alcohol **8** as a glycosyl acceptor under several conditions (Table 1). In procedure A, a mixture containing a glycosyl donor and the glycosyl acceptor was reacted with *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) at –20 °C. In procedure B, a similar mixture was treated with Me_2S_2-Tf_2O reagent at –40 °C. [12] In procedure C, the glycosyl donor was first pre-activated with diphenylsulfoxide (Ph_2SO) and trifluoromethanesulfonic anhydride (Tf_2O) in the presence of tri-*tert*-butylpyrimidine (TTBP) at –60 °C and then the glycosyl acceptor was added to the mixture.[13]

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

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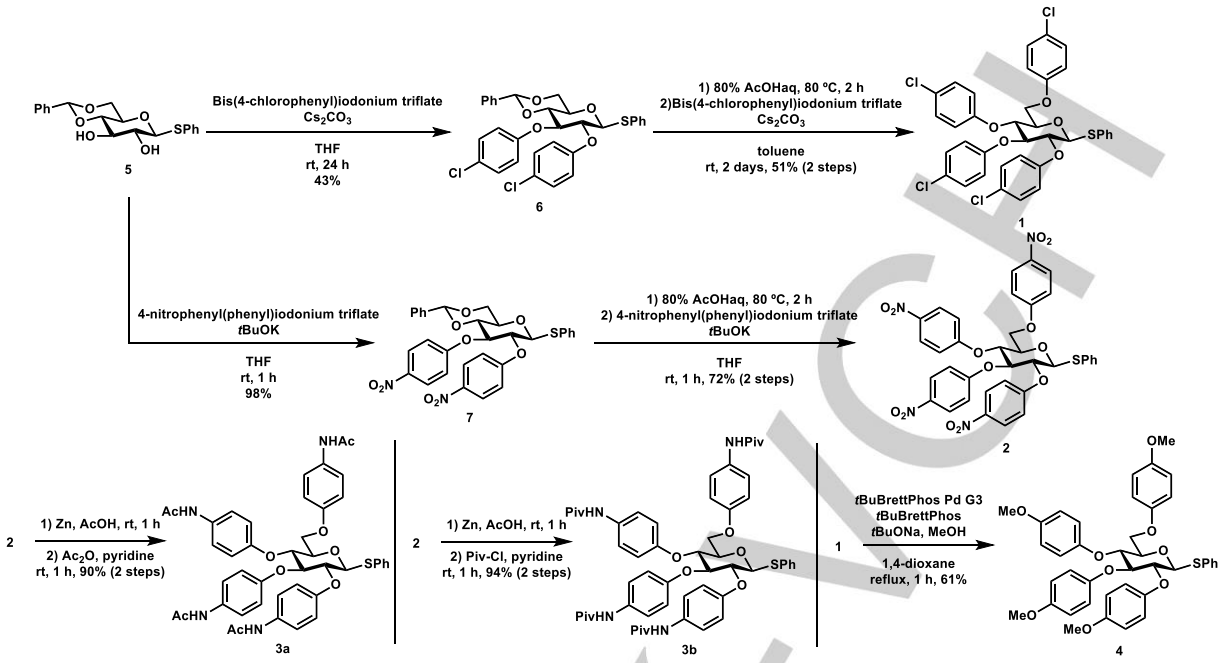
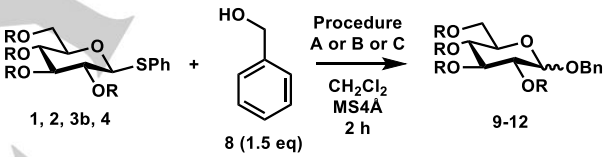
FULL PAPER

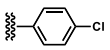
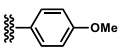
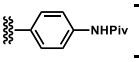
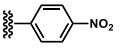


Scheme 1. Syntheses of tetra-*O*-arylated thioglycosides.

Glycosylation of 4-chlorophenyl (4-ClPhe) protected glycosyl donor **1** by procedures A and B afforded benzyl glycoside **9** with low stereoselectivity (Entries 1 and 2). On the contrary, the glycosylation by procedure C furnished the desired product in good yield with high β-selectivity (Entry 3). 4-Methoxyphenyl (MP) protected thioglycoside **4** was smoothly activated by procedure A to give benzyl glycoside **10** in good yield (Entry 4). However, when using procedure B and C, the presence of a powerful electrophilic reagent resulted in the modification of the MP moiety in **4** without getting desired compound **10** (Entries 5 and 6). The glycosylation of 4-pivaloylaminophenyl (PAP) protected thioglycoside **3b** gave the desired product **11** with low stereoselectivity by procedure A (Entry 7) and with high β-selectivity by procedure B (Entry 8), whereas procedure C caused decomposition of **3b** due to the activation of the amide moiety in the PAP group (Entry 9). 4-Nitrophenyl (NP) protected thioglycoside **2** showed high β-selectivity in procedure A (Entry 10) and the use of procedure B led to an improvement of the β-selectivity (Entry 11). Moreover, the glycosylation of **2** by procedure C afforded the desired product **12** in good yield with exceptionally high β-selectivity (Entry 12). In general, the β-selectivity was found to increase as the temperature decreased, which suggests that the glycosylation proceeds most likely via an S_N2-like reaction of the α-glycosyl triflate intermediates. It was also apparent that the electron-withdrawing character of the phenyl groups affected the selectivity of glycosylation.

Table 1. Glycosylation of *O*-aryl protected thioglycosides.



Entry	Donor	Method	Products	Isolated yield	α/β Ratio
1	R =  **1**	A[a]	**9**	65%	1 : 1.2
2		B[b]	**9**	64%	1 : 1.4
3		C[c]	**9**	83%	1 : 7.5
4	R =  **4**	A	**10**	86%	1 : 1.2
5		B	**10**	0%	-
6		C	**10**	0%	-
7	R =  **3b**	A	**11**	55%	1 : 1.5
8		B	**11**	57%	1 : 7.3
9		C	**11**	0%	-
10	R =  **2**	A	**12**	70%	1 : 5.7
11		B	**12**	72%	1 : 9.3
12		C	**12**	87%	1 : 27

[a] Procedure A : NIS, TfOH, –20 °C. [b] Procedure B : Me_2S_2-Tf_2O, –40 °C.
[c] Procedure C : Ph_2SO, Tf_2O, TTBP, –60 °C.

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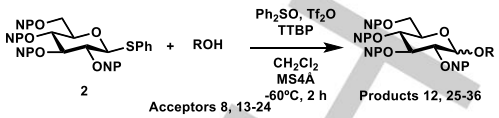
Since the electronic environment of the anomeric position can be assessed by the chemical shift of the anomeric proton observed in the ^{1}H-NMR spectra, the stereoselectivity outcomes were plotted against the chemical shift values of the 1-proton of thioglycosides **1**, **2**, **3b**, and **4** (Figure S1). From this result, it can be extracted that the chemical shifts of the 1-proton were downfield shifted as the electron-withdrawing effect of the protecting group increased; thus, the 1-proton of the compound bearing NP appeared at 4.98 ppm, that with PAP at 4.87 ppm, with 4-ClPhe at 4.85 ppm, and with MP at 4.85 ppm. The β-selectivity was found to increase linearly as the chemical shifts increased.

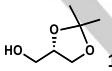
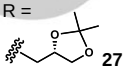
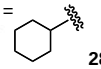
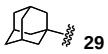
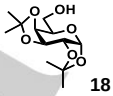
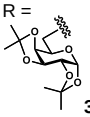
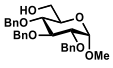
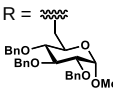
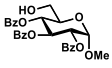
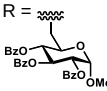
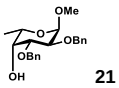
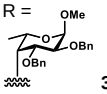
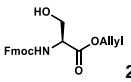
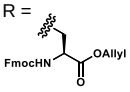
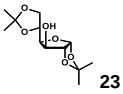
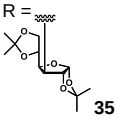
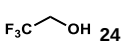
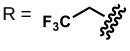
Wong *et al.* reported the correlation between the chemical shifts of the anomeric protons and the reactivity of the glycosyl donors.[14] For example, glycosyl donors possessing upfield-shifted anomeric protons showed high reactivity. On the other hand, the relationship between the stereoselectivity and the chemical shift of the proton has been rarely reported. Jensen *et al.* reported the effect of para-substituted benzyl-type protecting groups on the reactivity of thioglycoside glycosyl donors; glycosyl donors having electron-donating substituents showed higher reactivity than those having electron-withdrawing substituents, whereas the β-selectivity decreased by protection with substituted benzyl groups having electron-withdrawing groups.[15] Notably, our results regarding the stereoselectivity reveal the opposite tendency, and the glycosyl donor having NP groups exhibited the highest β-selectivity.

The scope and limitations of the glycosylation using the NP protected glycosyl donor **2** were then investigated by using methanol **13**, 1-butanol **14**, glycerol derivative **15**, cyclohexanol **16**, 1-adamantanol **17**, galactopyranose **18**, glucopyranoside **19**, another glucopyranoside **20**, fucopyranoside **21**, serine derivative **22**, glucofuranose **23**, and 2,2,2-trifluoroethanol (TFE) **24** as glycosyl acceptors (Table 2). The glycosylation of **13**, **14**, and **15**, which have a primary hydroxy group, afforded the desired products **25**, **26**, and **27** in high yields with high β-selectivities (Entries 2-4). The glycosylation of acceptors **16** and **17** having secondary and tertiary hydroxy groups also proceeded smoothly to give compound **28** and **29** with high β-selectivities in good yields (Entries 5, 6). The glycosylation of several sugars **18**, **19**, **20**, and **21**, and serine **22** gave the desired disaccharides **30**-**33** and sugar amino acid **34**, respectively, in moderate yields with high β-selectivities (Entries 7-11). Conversely, the glycosylation of glucofuranose **23** and TFE **24** showed α-selectivities probably owing to the low nucleophilicity of acceptors (Entries 12, 13).[16]

To elucidate the mechanism of this β-selective reaction, we examined the glycosylation with several glycosyl donors (Table 3). The glycosylation with benzyl protected thioglycoside **37** as a reference in procedure C, was carried out to afford product **43** with low stereoselectivity (Entry 1). The glycosylation reactions using partially NP protected glycosyl donors were then examined (Entries 2-4). It was found that the glycosylation of mono-*O*-NP protected thioglycoside **38** and di-*O*-NP protected thioglycoside **7** proceeded with low and moderate β-selectivity, respectively. In contrast, with tri-*O*-NP protected thioglycoside **39** afforded **46** with high β-selectivity.

Table 2. Glycosylation of NP protected thioglycosides.



Entry	Acceptor	Products	Isolated yield	α/β Ratio
1	benzyl alcohol **8**	R = Bn **12**	87%	1 : 27
2	methanol **13**	R = Me **25**	80%	1 : 30<
3	1-butanol **14**	R = Bu **26**	77%	1 : 30<
4	 **15**	R =  **27**	62%	1 : 30<
5	Cyclohexanol **16**	R =  **28**	80%	1 : 30<
6	1-Adamantanol **17**	R =  **29**	77%	1 : 30<
7	 **18**	R =  **30**	91%	1 : 13
8	 **19**	R =  **31**	65%	1 : 30<
9	 **20**	R =  **32**	68%	1 : 25
10	 **21**	R =  **33**	57%	1 : 7.8
11	 **22**	R =  **34**	46%	1 : 30<
12	 **23**	R =  **35**	48%	3.6 : 1
13	 **24**	R =  **36**	83%	2.5 : 1

The anomer ratio was determined by HPLC (UV350 nm).

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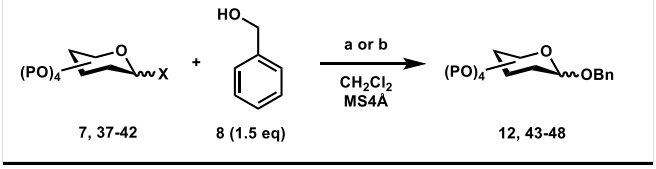
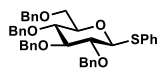
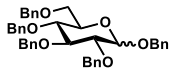
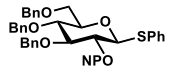
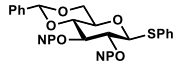
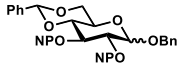
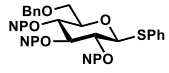
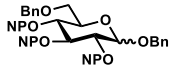
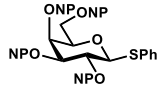
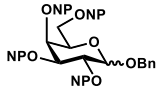
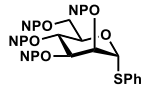
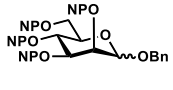
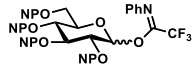
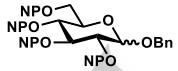
Table 3. Glycosylation of several glycosyl donors.



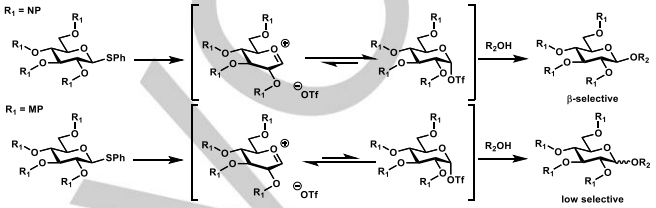
Entry	Donor	Products	Isolated yield	α/β Ratio
1[a]	 **37**	 **43**	85%	1 : 1.9
2[a]	 **38**	 **44**	65%	1 : 1.2
3[a]	 **7**	 **45**	77%	1 : 4.0
4[a]	 **39**	 **46**	58%	1 : 16
5[a]	 **40**	 **47**	88%	1 : 1.2
6[a]	 **41**	 **48**	92%	1.3 : 1
7[b]	 **42**	 **12**	51%	1 : 6.0

[a] Ph_2SO, Tf_2O, TTBP, –60 ºC. [b] $BF_3{\cdot}OEt_2$, –60 ºC.

On the other hand, NP protected galactosyl donor **40** or mannosyl donor **41** afforded the desired products with low stereoselectivities following procedure C, due to the steric effects of axial hydroxy groups (Entries 5, 6). For 2,2,2-trifluoro-*N*-phenyl acetimidate donor[17] **42**, the glycosylation was carried out in the presence of a non-triflate based Lewis acid (Entry 7). The moderate β-selectivity was obtained through activation with $BF_3{\cdot}OEt_2$ via S_N2-like displacement of α-glycosyl imidate.

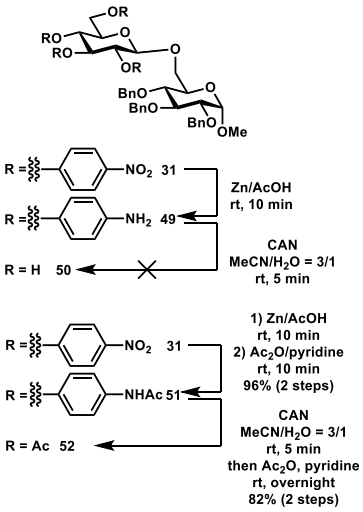
These results indicated that the β-selectivity increased with the number of NP groups. Furthermore, a linear correlation was observed between β-selectivity and the chemical shifts of the anomeric protons of thioglysides **2**, **37**, **38**, and **39**, but not of **7**, **40**, **41** having different steric environments (Figure S2).

The proposed reaction mechanism is described in Scheme 2, according to which the electron-withdrawing NP groups destabilize the oxocarbenium ion and promote the formation of an α-glycosyl triflate. The glycosylation proceeds via S_N2-like displacement of the α-glycosyl triflate, affording high β-selectivity. On the other hand, electron-donating groups such as MP stabilize the oxocarbenium ion and promote the S_N1 pathway, resulting in low selectivity. Therefore, it can be concluded that the stereoselectivity of the glycosylation can be controlled by the substituents on the aryl protecting groups.



Scheme 2. Proposed reaction mechanism.

Finally, we investigated the removal of the NP group from compound **31** (Scheme 3). Thus, reduction of the nitro moiety of **31** with zinc afforded aminophenyl derivative **49**.[18] Next, we tested the oxidative cleavage of the aminophenyl group by using ammonium hexanitratocerate (IV) (CAN), however, decomposition of the electron-rich aminophenyl group occurred. Then we examined the acetamidophenyl group as deprotection substrate. Acetamidophenyl derivative **51** was obtained from compound **31** in good yield by reduction of the nitro groups followed by acetylation. Cleavage of the acetamidophenyl group by CAN and subsequent acetylation of the hydroxy groups proceeded smoothly to give the desired compound **52** in good yield.



Scheme 3. Removal of NP group.

Conclusions

In summary, we have developed several *O*-aryl-protected glycosyl donors and investigated their stereoselectivity in the glycosylation reaction. In particular, NP protected thioglycoside showed high β-selectivity at low temperature, which indicates that the reaction probably proceeds via an S_N2-type reaction that involves an α-glycosyl triflate. Finally, the NP group can be removed by reduction of the nitro group and acylation, followed by CAN oxidation. Further studies on the reactivity of *O*-arylated glycosyl donors and their application are currently in progress in our laboratory.

Experimental Section

The synthetic procedures and characterization of the compounds studied herein can be found in the Supporting Information.

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Keywords: Glycosylation • *O*-aryl protection • 4-nitrophenyl group

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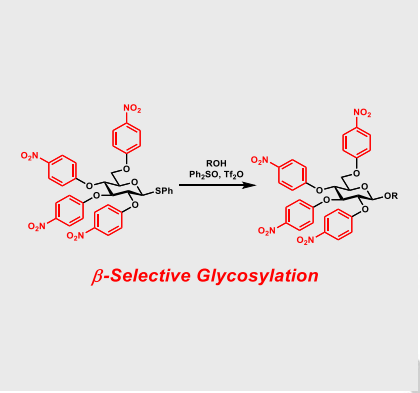
FULL PAPER

Glycosylation using *O*-aryl protected glycosyl donors is described. Highly β-selective glycosylation was achieved using 4-Nitrophenyl (NP) protected thioglycosides. Because increasing the electron-withdrawing property of the *O*-aryl groups enhances β-selectivity, glycosylation probably proceeds via S_N2-like displacement from the corresponding α-glycosyl triflate.



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β-Selective glycosylation using *O*-aryl protected glycosyl donors